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(54) PROCESS FOR PRODUCING OPTICALLY ACTIVE MEVALONOLACTONE COMPOUND

(57) The process for preparing mevalonolactone compounds is carried out by means of batch system chromatography or a simulated moving bed chromatographic process using columns filled with an optical resolution filler comprising a polysaccharide derivative. The simulated moving bed chromatographic process comprises forming a circulation flow circuit comprising a plurality of columns endlessly connected in series; enforcing a fluid to flow through the circuit in one direction; providing the column series alternately with an inlet port through which the fluid is introduced into the column in the flow direction and with an outlet port, through which the fluid is taken out; intermittently shifting activation of the inlet port and the outlet port in the direction of the fluid flow; introducing a solution containing a racemic mevalonolactone compound and an eluent through an inlet port into the circuit; and simultaneously taking out a solution rich in the weakly adsorbable substance and a solution rich in the strongly adsorbable and desorbed substance through the outlet port.

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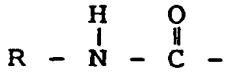
12 carbon atoms, an alkylthio group having 1 - 12 carbon atoms, a cyano group, a halogen atom, an acyl group having 1 - 8 carbon atoms, an acyloxy group having 1 - 8 carbon atoms, a hydroxy group, an alkoxycarbonyl group having 1 - 12 carbon atoms, a nitro group, an amino group and an alkylamino group having 1 - 8 carbon atoms; and X stands for a hydrocarbon group having 1 - 4 carbon atoms, which may contain a double bond or triple bond.

The invention described in claim 3 is a process for preparing an optically active mevalonolactone compound comprising forming a circulation flow circuit comprising a plurality of columns filled with an optical resolution filler and endlessly connected in series; enforcing a fluid to flow through the circuit in one direction; providing each with an inlet port through which the fluid is introduced into the column in the flow direction and with an outlet port, through which the fluid is taken out; intermittently shifting the working position of the inlet port and a suitably-spaced outlet port in the direction of the fluid flow; introducing a solution containing a racemic mevalonolacton compound and an eluent through an inlet port into the circuit; and simultaneously taking out a solution rich in the weakly adsorbable and a solution rich in the strongly adsorbable through the outlet port.

The invention described in claim 4 is a process for preparing an optically active mevalonolactone compound as described in claim 3, wherein the optical resolution filler is one selected from a group consisting of particles of a polysaccharide ester derivative, particles of a polysaccharide carbamate derivative and particles of a support which carries a polysaccharide ester derivative and/or a polysaccharide carbamate derivative.

The invention described in claim 5 is a process for preparing an optically active mevalonolacton compound as described in claim 4, wherein the polysaccharide ester derivative and the polysaccharide are those in which part of or all of the hydrogen atoms on the hydroxy groups or amino groups of the polysaccharide are substituted with any of the atom groups represented by the following chemical formulas (1) to (4):



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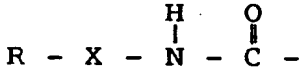

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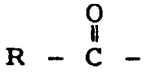

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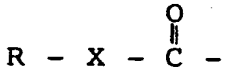


(4)

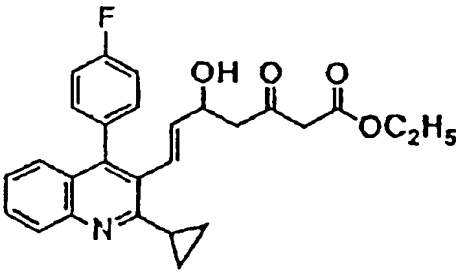
wherein R stands for an aromatic group which may contain a hetero atom and may be unsubstituted or substituted with at least one selected from a group consisting of an alkyl group having 1 - 12 carbon atoms, an alkoxy group having 1 - 12 carbon atoms, an alkylthio group having 1 - 12 carbon atoms, a cyano group, a halogen atom, an acyl group having 1 - 8 carbon atoms, an acyloxy group having 1 - 8 carbon atoms, a hydroxy group, an alkoxycarbonyl group having 1 - 12 carbon atoms, a nitro group, an amino group and an alkylamino group having 1 - 8 carbon atoms; and X stands for a hydrocarbon group having 1 - 4 carbon atoms, which may contain a double bond or triple bond.

The invention described in claim 6 is a process for preparing an optically active mevalonolacton compound as described in any of claims 1 to 5, wherein the optically active mevalonolactone compound is ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-5-hydroxy-3-oxo-6-heptenoate or ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6-heptenoate.

Mevalonolactone compounds handled in the process of the present invention are represented by a chemical formula (5)

(5)

wherein R is a carbocyclic aromatic group, heterocyclic aromatic group or fused ring heterocyclic aromatic groups hav-



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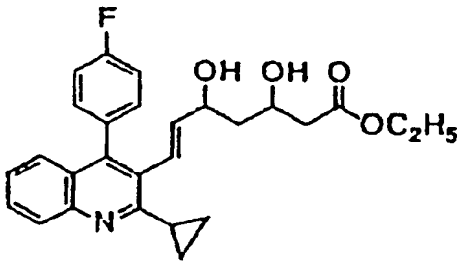

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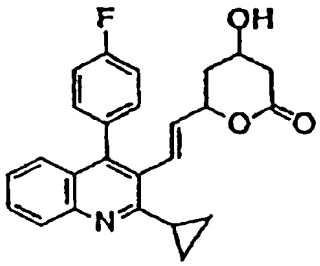


(10)

Now we will discuss the optical resolution fillers used in the present invention.

Various resolution fillers can be used without any limitation if they are able to optically separate a racemic mixture of optically active mevalonolactone compounds. Preferred optical resolution fillers usable in the present invention are selected from a group consisting of particles of a polysaccharide ester derivative, particles of a polysaccharide carbamate derivative and particles on which a polysaccharide ester derivative and/or a polysaccharide carbamate derivative is supported.

The polysaccharide of the above-mentioned polysaccharide ester derivative and polysaccharide carbamate derivative can be any of naturally occurring polysaccharide, modified natural polysaccharide, synthesized polysaccharide as well as oligo sugars. They can be used without any limitation insofar as they are optically active.

Specific examples of the polysaccharides are: α-1,4-glucane (starch, glycogen, amylose), β-1,4-glucan (cellulose), α-1,6-glucan (dextran), β-1,3-glucan (curdlan, schizophylan), α-1,3-glucan, β-1,2-glucan (Crawn Gall polysaccharide) α-1,6-mannan, β-1,4-mannan, β-1,2-fructan (inuline), β-2,6-fructan (levan), β-1,4-xylan, β-1,3-xylan, β-1,4-chitosan, β-1,4-N-acetylchitosan (chitin), α-1,3-1,6-glucan (mutan), pullulan, agalose, arginic acid, etc.

The number average polymerization degree (an average number of pyranose or furanose rings) of these polysac-

is usually 1 - 100 wt% of the amount of the support, preferably 5 - 50 wt%. With not more than 1 wt%, optical resolution of a mevalonolactone may not be satisfactorily effected. If the amount is in excess of 100 wt%, corresponding effect may not be expected.

In the process of this invention, as organic solvents, alcohols such as methanol, ethanol, propanol, etc., hydrocarbons such as hexane as well as a mixed solvent such as a mixture of a hydrocarbon and an alcohol, can be used as eluent for both batch system chromatography and simulated moving bed chromatographic process. A preferred eluent can be suitably selected depending upon the species of the mevalonolactone compound subjected to optical resolution.

The batch system chromatography employed in the present invention is known per se and commonly used.

The simulated moving bed chromatographic process comprises forming a flow circuit by endlessly connecting in series a plurality of columns filled with an optical resolution filler; enforcing a fluid to circulate through the circuit in one direction; providing the columns with an inlet port through which the fluid is introduced into the circuit in the direction of the fluid flow and an outlet port through which the liquid is taken out; shifting the working positions of the inlet port and a suitably spaced outlet port intermittently in the direction of the fluid flow; introducing a solution containing a racemic compound which should be optically separated and an eluent through an inlet port; and simultaneously taking out a solution rich in the weakly adsorbed substances and a solution rich in the strongly adsorbed and desorbed substances through an outlet port.

In the simulated moving bed chromatographic process, a simulated moving bed, which comprises a plurality (12 or 8, for instance) of columns which are serially arranged in the circuit as shown in Fig. 1, is used. The fluid flows only in one direction. The number of the unit columns is not limited to the numbers indicated above but it can be suitably selected depending upon operation scale, consideration on chemical engineering conditions, etc.

In this simulated moving bed, an inlet port for an eluent; an outlet port through which a solution containing an optical isomer easily adsorbable by the filler (extract) is taken out; an inlet port through which a solution containing a racemic compound is introduced; and an outlet port through which a solution containing an optical isomer not easily adsorbed by the filler (raffinate) is taken out are assigned in this order in the direction of fluid flow; and the working positions of these ports are intermittently and successively shifted in the direction of fluid flow.

In a simulated moving bed as shown in Fig. 1, an inlet port for introducing the eluent; an outlet port for taking out the extract; an inlet port for introducing a solution containing a racemic compound; and an outlet port for taking out the raffinate are respectively assigned at every third unit column. In order to intermittently and successively shift the role of the inlet ports and outlet ports, rotary valve, electromagnetic valve, air-actuated valve, etc. are used.

Separation by adsorption of a mevalonolactone compound in the simulated moving bed chromatographic process is basically effected by continuously and cyclically carrying out the adsorption step, the concentration step, the desorption step and the eluent recovery step.

(1) Adsorption step

A mevalonolactone compound in the form of racemic mixture is made contact with the optical resolution filler, whereby an optical isomer which is strongly adsorbed by the filler (the adsorbable) is adsorbed, and another optical isomer which is not easily adsorbed by the filler (the weakly adsorbable) is recovered together with the eluent.

(2) Concentration step

The optical resolution filler which has adsorbed the adsorbable is contacted with a portion of the extract described below and the weakly adsorbable which is retained on the optical resolution filler is expelled and thus the adsorbable is concentrated.

(3) Desorption step

The optical resolution filler which has adsorbed the strongly adsorbable is contacted with the eluent, the adsorbable is expelled from the filler and taken out of the simulating moving bed together with the eluent as extract.

(4) Eluent recovery step

The optical resolution filler which contains substantially the eluent only is contacted with a portion of the raffinate and a portion of the eluent contained in the optical resolution filler is recovered as an eluent recovery.

The process is more specifically described with reference to the attached drawing.

In Fig. 1, unit columns 1 - 12 are filled with an optical resolution filler and they are mutually connected with fluid passages. The eluent is introduced through an eluent supply conduit 13: the extract is taken out through an extract conduit 14, the solution containing a racemic compound is supplied via conduit 15, the raffinate is taken out through a raffinate conduit 16 and the fluid is recirculated through a recirculation conduit 17 by means of a pump 18.

In the state of the unit columns 1 - 12 and conduits 13 - 16 as indicated in Fig. 1, desorption is effected in unit columns 1 - 3, concentration is effected in unit columns 4 - 6, adsorption is effected in unit columns 7 - 9 and eluent recovery is effected in unit columns 10 - 12.

In the simulated moving bed like this, the working positions of the eluent supply conduit, the conduit which supplies a solution containing a racemic compound, respective extract conduits are shifted one unit column by one unit column in the fluid flow direction at a constant time interval by operation of valves.

Example 3

Using a column 0.46 cm in inner diameter and 25 cm in length filled with silica gel supporting cellulose triphenylcarbamate ("CHIRALCEL OC" marketed by Daicel Chemical Industries, Ltd.), the (3R,5S) body and the (3S, 5R) body of ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoate were optically separated. Conditions of liquid phase chromatography, retention time of the two isomers, capacity factor, separation factor, resolution factor and order of elution are indicated in Table 1.

Example 4

Using a column 0.46 cm in inner diameter and 25 cm in length filled with silica gel supporting cellulose tris(3,5-dimethylphenylcarbamate) ("CHIRALCEL OD" marketed by Daicel Chemical Industries, Ltd.), the (3R,5S) body and the (3S, 5R) body of ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoate were optically separated. Conditions of liquid phase chromatography, retention time of the two isomers, capacity factor, separation factor, resolution factor and order of elution are indicated in Table 1.

Example 5

Using a column 0.46 cm in inner diameter and 25 cm in length filled with silica gel supporting cellulose tris(p-methylphenylcarbamate)("CHIRALCEL OG" marketed by Daicel Chemical Industries, Ltd.), the (3R,5S) body and the (3S, 5R) body of ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoate were optically separated. Conditions of liquid phase chromatography, retention time of the two isomers, capacity factor, separation factor, resolution factor and order of elution are indicated in Table 1.

Example 6

Using a column 0.46 cm in inner diameter and 25 cm in length filled with silica gel supporting amylose tris((s)-1-phenylethylcarbamate) ("CHIRALPAK AS" marketed by Daicel Chemical Industries, Ltd.), racemic ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-5-hydroxy-3-oxo-6-heptenoate was optically separated. Conditions of liquid phase chromatography, retention time of the two isomers,

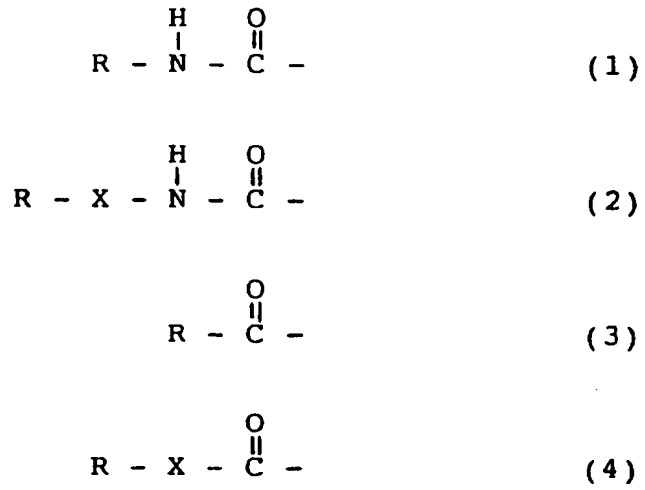
Table 2

		Example 6	Example 7
Filler		CHIRALCEL AS	CHIRALCEL AD
Conditions	Eluent (vol.ratio)	H/I=90/10	H/I=90/10
	Flow rate (ml/min.)	1.0	1.0
	Column temp. (°C)	5	40
Detection		UV detector Wave length: 254 nm	
Parameters	Retention time (ml/min.)	22.5 37.7	8.2 8.9
	Capacity factor (k_1')	6.51	1.74
	Separation factor (a)	1.78	1.12
	Resolution factor (Rs)	1.56	0.51

capacity factor, separation factor, resolution factor and order of elution are indicated in Table 2.

Example 7

Using a column 0.46 cm in inner diameter and 25 cm in length filled with silica gel supporting amylose tris(3,5-dimethylphenylcarbamate) ("CHIRALPAK AD" marketed by Daicel Chemical Industries, Ltd.), racemic ethyl 7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-5-hydroxy-3-oxo-6-heptenoate were optically separated. Conditions of liquid phase chromatography, retention time of the two isomers, capacity factor, separation factor, resolution factor and order of elution are indicated in Table 2.



(1)

(2)

(3)

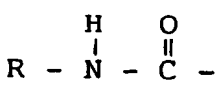
(4)

wherein R stands for an aromatic group which may contain a hetero atom and may be unsubstituted or substituted with at least one selected from a group consisting of an alkyl group having 1 - 12 carbon atoms, an alkoxy group having 1 - 12 carbon atoms, an alkylthio group having 1 - 12 carbon atoms, a cyano group, a halogen atom, an acyl group having 1 - 8 carbon atoms, an acyloxy group having 1 - 8 carbon atoms, a hydroxy group, an alkoxycarbonyl group having 1 - 12 carbon atoms, a nitro group, an amino group and an alkylamino group having 1 - 8 carbon atoms; and X stands for a hydrocarbon group having 1 - 4 carbon atoms, which may contain a double bond or triple bond.

3. A process for preparing an optically active mevalonolacton compound comprising forming a circulation flow circuit comprising a plurality of columns filled with an optical resolution filler and endlessly connected in series; enforcing a fluid to flow through the circuit in one direction; providing each with an inlet port through which the fluid is introduced into the column in the flow direction and with an outlet port, through which the fluid is taken out; intermittently shifting the working position of the inlet port and a suitably-spaced outlet port in the direction of the fluid flow; introducing a solution containing a racemic mevalonolactone compound and an eluent through an inlet port into the circuit; and simultaneously taking out a solution rich in the weakly-adsorbable and a solution rich in the strongly adsorbable through the outlet port.

4. The process for preparing an optically active mevalonolactone compound as described in claim 3, wherein the optical resolution filler is one selected from a group consisting of particles of a polysaccharide ester derivative, particles of a polysaccharide carbamate derivative and particles of a support which carries a polysaccharide ester derivative and/or a polysaccharide carbamate derivative.

5. The process for preparing an optically active mevalonolacton compounds as described in claim 4, wherein the polysaccharide ester derivative and the polysaccharide are those in which part of or all of the hydrogen atoms on the hydroxy groups or amino groups of the polysaccharide are substituted with any of the atom groups represented by the following chemical formulas (1) to (4):



(1)

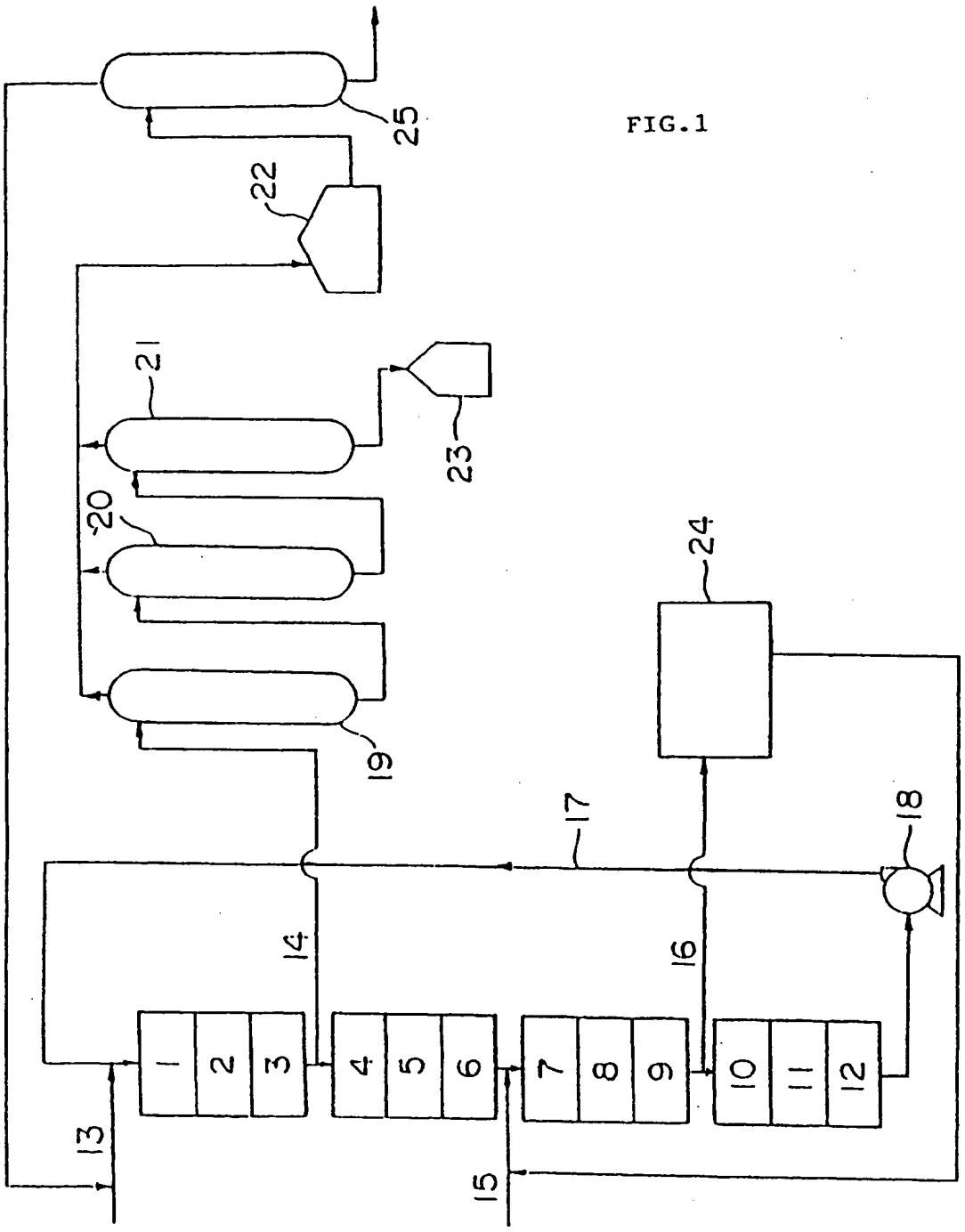


FIG.1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP95/00251

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 C07C59/48, 59/90, 51/47, 69/732, 69/738, 67/56, C07D215/14, 309/30, 405/06//C07M7:00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 C07C59/48, 59/90, 51/47, 69/732, 69/738, 67/56, C07D215/14, 309/30, 405/06//C07M7:00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP, 5-148237, A (Nissan Chemical Industries, Ltd.), June 15, 1993 (15. 06. 93) & EP, 520406, A1 & US, 5284953, A & CA, 2072162, A	1 - 6
Y	JP, 62-211552, A (Daicel Chemical Industries, Ltd.), September 17, 1987 (17. 09. 87)(Family: none)	1, 2, 4-6
Y	JP, 5-70599, A (Daicel Chemical Industries, Ltd.), March 23, 1993 (23. 03. 93) & WO, 92-15635, A1 & EP, 527236, A1 & US, 5354852, A	1, 2, 4-6
Y	JP, 60-226829, A (Daicel Chemical Industries, Ltd.), November 12, 1985 (12. 11. 85) & EP, 156382, A & US, 4879038, A & US, 4966694, A & US, 5017290, A	1, 2, 4-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
May 18, 1995 (18. 05. 95)	May 30, 1995 (30. 05. 95)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)